EXHIBIT A

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CLINICAL STUDIES WITH GALANTHAMINE

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CONTENTS

Summary

The use of galanthamine in Alzheimer's disease dates back to 1986. A small-scale open pilot study was conducted with 9 patients at the psychiatric clinic in Gugging, Austria, in the following year. Two other pilot studies, performed in Austria and Great Britain, showed mixed results that could be explained by weaknesses of their designs; however, those were sufficient to arouse attention.

In a subsequent multicenter, placebo-controlled study, 167 Alzheimer patients entered a 3-week single-blind, dose-titration phase, with an upper limit of 50 mg galanthamine per day. The 141 drug responders were randomized either to continue galanthamine therapy, or to receive placebo for the following 10-week double-blind phase. At endpoint, those who had remained on galanthamine had improved by an additional 1.66 ADAS-Cog points, while those switched to placebo had deteriorated by 1.40 points.

Several other studies, some still ongoing, and data from Austria where galanthamine has been licensed for mild to moderately severe Alzheimer's disease, confirm that the optimal dose range is between 30 and 45 mg/day, that side effects are mild and transient, and do not include hepatotoxicity. After 3 years of continuous therapy, a group of outpatients who received galanthamine in addition to other drug treatment still showed cognitive benefit relative to a control group. Therefore, galanthamine should be regarded as an excellent representative of the emerging second-generation acetylcholinesterase inhibitors.

Introduction

Since the ground-breaking work by Perry's group almost 20 years ago (1), the close association between central cholinergic deficiency and cognitive impairments has been extensively demonstrated. Similar to supplementation with L-dopamine to compensate for the dopaminergic deficit in Parkinson's disease, the rationale for using cholinergic drugs in Alzheimer's disease (AD) is to reverse the functional deficits in cholinergic neurotransmission. Secondary effects of such a treatment might include an increase of regional cerebral blood flow in the brain (2). However, not all AD patients can expect equal benefit, as

the clinical (3) and genetic (4) heterogeneity of this condition is well established.

At the present time, the indirect strategy of inhibiting the catabolic enzyme, acetylcholinesterase, in cortical synapses is the only approach that is widely accepted and practiced. Of several chemical entities that were identified and investigated during the initial period, tetrahydroaminoacridine (tacrine, Cognex®) was the first acetylcholinesterase inhibitor (AChEI) to be marketed worldwide for the symptomatic treatment of cognitive deficiency in mild and moderate AD (5, 6).

Tacrine, however, is far from being therapeutically ideal. It is characterized by a pronounced first-pass metabolism, resulting in a low and highly variable oral bioavailability that could be as low as 17% (7). A short plasma clearance time of < 2 hours, a pharmacology involving several secondary metabolites with AChEI activity (8), its incompletely understood effect on monoaminergic neurotransmission (9), and above all its pronounced hepatotoxic effect (10, 11), which necessitates serum transaminase monitoring every other week, have contributed to creating the impression of a first generation drug in its class, a term coined by Giacobini (12). Side effects, and hence compliance, are often limiting factors in tacrine therapy as many patients cannot permanently tolerate doses of 120-160 mg/day that would produce the most pronounced cognitive improvements (13). Instead, 80 mg/day is the dose most frequently used for long-term treatment, evidently compromising the efficacy of therapy.

Several AChEIs with pharmacologically more acceptable drug profiles are now becoming available, and should be appropriately called second generation drugs for the symptomatic treatment of AD. As a group, they are characterized by an extended biological half-life, a reduced rate of side effects and the potential to create steady-state conditions of acetylcholinesterase inhibition at the levels required for long-term treatment. These properties should pave the way for a therapy that stabilizes the enzyme activity at 30-60% of its baseline level, which is the therapeutic window for AChEIs that has been postulated by Becker *et al.* (14) on the basis of a generalized dose-response curve (Fig. 1). Among the most widely known of these advanced AChEIs are eptastigmine, metrifonate, donepezil hydrochloride (also known as E-2020), SDZ-ENA-713 (Exelon®) and galanthamine.

With its unique multidecade record of safe use in humans, an elimination time of about 6 hours, a tolerable cholinergic side effect profile, a complete lack of hepatotoxicity, and a high selectivity for acetylcholinesterase as opposed to butyrylcholinesterase (15), galanthamine should be a very favorable alternative to tacrine.

Case and Pilot Studies

The notion that it might be possible to exploit the well-established central cholinergic effects of galanthamine for the treatment of AD can be traced back to the psychiatric ward at Ybbs a.d. Donau in Austria, where the first favorable case studies were reported in 1986 (16).

Based on these tentative results, a small-scale open pilot study was conducted at the regional psychiatric clinic in Gugging, Austria. In 1987 (17). After a 2-week washout period during which all psychotropic medication was discontinued, the 9 presumable Alzheimer patients (age range, 61-89 yr; Hachinski ischemic score below 3) who were included in this protocol were started on daily doses of 3 x 5 mg Nivalin® (Waldheim Pharmazeutika's galanthamine hydrobromide tablets), and after 1 week the dose was increased to 30 mg/day for 7 additional weeks. At endpoint, 6 patients demonstrated improvements in the Mini-Mental State Evaluation, the Syndrome Brief Test and the Geriatric Rating Scale. Significant improvements in quality of life and day-to-day performance was reported for 3 patients. Overall, 3 participants (33%) had consistent improvements in all recorded parameters. No adverse side effects were reported during the entire evaluation period of 2 months, and drug monitoring data indicated no deviations outside the reference ranges. A rise in alkaline phosphatase levels in 2 patients, which was clinically insignificant, might have been attributed to collateral antibiotic medication.

At about the same time, another group at the Free University Berlin conducted a case study which, although concerned with only 1 AD patient, was of particular value because it lasted 5 months, monitored rebound effects from transient discontinuation of drug therapy and included monitoring of pharmacological parameters such as galanthamine plasma levels and acetylcholinesterase inhibition (18, 19). The authors concluded that galanthamine was well tolerated without hepatotoxic effects, and was correlated with physician-rated clinical improvement whenever 50% inhibition of plasma acetylcholinesterase was achieved.

During the 2 years it took to publish the reports on the studies performed in Vienna and Berlin, a United States patent for the use of galanthamine in AD was issued that did not make reference to any peer reviewed report on its clinical use (20). It might be worth noting that the efficacy of the substance in experimentally induced amnesia had been published in a Soviet journal as early as 1976 (21).

DRUGS OF TODAY Vol 33, No 4 1997

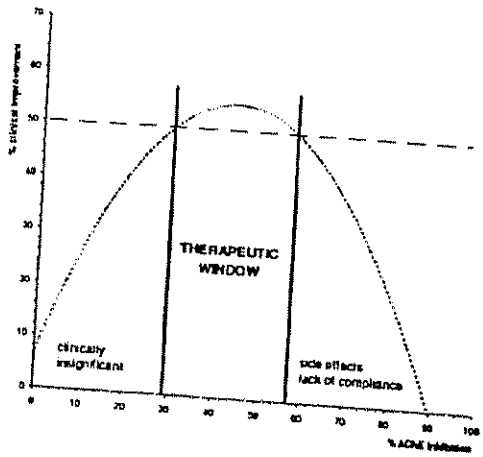

Fig. 1. Schematic representation of the dose-response relationship in acetylcholinesterase inhibitor treatment of Alzheimer's disease according to Becker *et al.* A 50% or better clinical improvement will result only when 30-60% relative enzyme inhibition is achieved; at higher concentration, drug resorption and compliance issues will reduce efficacy of therapy.

A second open pilot study at the Vienna Memory Clinic (22) enrolled 18 patients with probable AD according to the NINCS-ADRDA criteria (23) who received mean daily doses of 30 mg galanthamine for a nominal period of 24 weeks. At the first assessment at 8 weeks, no statistically significant changes were noted, but 10 patients who were considered to be responders nevertheless completed the study course. Six of these patients were continued on their best individual dose (30-50 mg/day) for a total of 16 months, at which point all had favorable results.

Unfortunately, the test battery employed in this early investigation did not include properly validated and internationally acknowledged cognitive tests, such as the Alzheimer Disease Assessment Scale (ADAS) (24) or the Mini-Mental State Examination (MMSE) (25). Nevertheless, the study corroborated the notion that there exists a relatively homogenous subgroup of about one-third of the patient sample with potential for improvement in terms of emotional stability, coping with everyday life requirements and social competence under galanthamine therapy. These noncognitive improvements were clearly drug-related and were partially lost when galanthamine therapy was temporarily interrupted. One possible explanation would be that these patients suffer from a relatively uniform cholinergic deficit, while signal transduction based on other neurotransmitters is relatively intact.

Under the protocol of another open pilot study conducted in Great Britain (26), 19 AD patients received galanthamine in daily doses of either 30-40 mg or 45-60 mg for two 6-week periods separated by a 3-week, drug-free interval. The second of these two study arms employed higher doses than had been used at any time before. The high incidence of side effects that was recorded in the 45-60 mg group, together with a dropout rate of 37%, was therefore expected. Overall, only 11 patients completed the entire study course. No deterioration in routine laboratory parameters was seen and the only clinically significant event was rash in one patient.

The ADAS cognitive score showed 5.4% improvement during the first 6 weeks, and deteriorated 1.8 points during the 3-week intermediate washout phase. An additional gain of 2.5 points relative to the elevated intermediate baseline was noted during the second therapy interval, resulting in a total gain of 6.0 points on the ADAS-Cog scale relative to the absolute baseline ($p < 0.03$). The MMSE showed a similar pattern of therapy-related improvement totaling 1.7 ± 0.7 points at the end of the study ($p < 0.04$), while only limited gains (without statistical significance) were achieved on the Clinical Global Impression of Change (CGIC) scale. Overall, the 30-40 mg/day treatment course was clinically more effective than the 45-60 mg scheme, probably

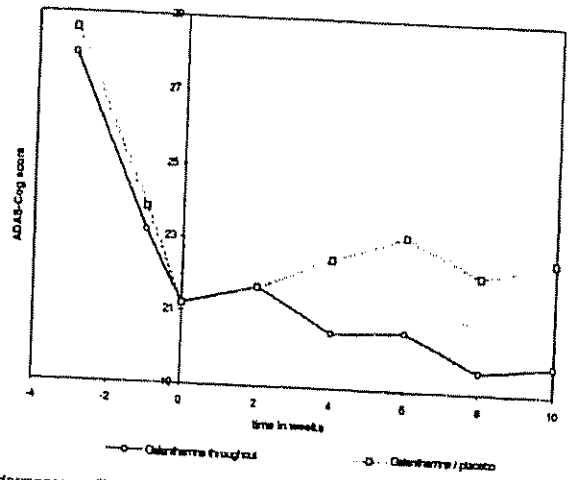

Fig. 2. Cognitive performance profile of 141 galanthamine responders in the multicenter study published by Berzewski *et al.* (ref. 27) Solid line, all-time galanthamine patients at best individual dose; dotted line, patients who received galanthamine only until t = 0, and were then randomized to the placebo group. Lower ADAS-Cog scores indicate better performance.

because of compliance and drug resorption issues in the high-dose group.

Clinical Trials

These early pilot studies, limited as they were in terms of methodology and sample size, aroused a measure of attention. In 1989 a large pharmaceutical company sponsored an international, multicenter, placebo-controlled study design (27). Following a washout phase of 2 weeks during which all psychotropic medications were discontinued, and an introductory phase that excluded prospective participants with strong response to placebo, 167 individuals with mild or moderate probable AD (according to NINCDS-ADRDA and DSM-III-R criteria) entered a 3-week, single-blind, dose-titration phase that started at 20 mg galanthamine per day. Dose increases in 10 mg increments every 3 days were allowed until the individual best dose was reached (as defined by AChE measurements in erythrocytes (28) which served as a surrogate marker), with an upper limit of 50 mg/day. In accordance with Becker's therapeutic window hypothesis, achieving a steady-state level of at least 40% acetylcholinesterase inhibition (relative to the pretherapy baseline) was attempted in every patient.

After the initial dose adjustment phase, the 141 patients who were considered drug responders (equivalent to 78% of those enrolled) had a dose-related improvement of 5.14 ± 0.53 ADAS-Cog points, which compares well with the 5.4 points improvement during the 6-week treatment in the study by Wilcock described above. Members of this responder subgroup were randomized either to continue galanthamine therapy at the individual best dose, or to be switched to placebo for the following 10-week, double-blind phase. At the end of the 13-week course, those who had remained on galanthamine had improved by an additional 1.66 ADAS-Cog points, while those switched to placebo had deteriorated by 1.40 points.

Overall, the cognitive performance of all-time galanthamine patients significantly exceeded (by 3 points) the level of those who had received active drug only for the first 3 weeks (Fig. 2). Again, the MMSE scores exhibited a behavior that was similar but not as pronounced: scores improved by 1.72 points during the dose optimization phase and were 2.5 points above baseline for drug responders at the end of the 13-week study course, while the placebo group had dropped 1.7 points below its baseline at this time. The results of the Syndrome Brief Test and the CGIC rating indicated the same trend. CGIC scores in particular were highly significant: 72% of the patients on galanthamine showed improvements on any level, and 30% were rated "much improved" or "very much improved". These results, which reflect a drug therapy effect in cognitive as well as

global evaluation scales, were basically in agreement with the Wilcock pilot study.

As had been expected from earlier experience, cholinergic side effects were dose-dependent, mild and transient. Nausea and vomiting were reported in 21% of a subgroup of 81 patients who received an average dose of 29.4 mg/day galanthamine, while these rates were 29% and 63% in patients receiving average daily doses of 34.7 and 37.9 mg, respectively. Other peripheral cholinergic symptoms included diarrhea and abdominal cramps (4% each), weight loss (1.2%), anorexia (3%) and other digestive disorders (0.6%). No clinically relevant changes were observed during the drug monitoring process.

Final review of the study data failed to reveal a correlation between cognitive improvement and drug dosage at endpoint ($r = 0.04$). The loss of the dose relationship that had been observed at the end of the initial selection and adjustment phase may be attributed to the fact that the double-blind phase continued at the individual best dose, or to an adaptive response of the cholinergic system, or a combination of both factors.

At this time, only limited information is available on an ongoing placebo-controlled study for which interim results were reported at the 5th International Conference on Alzheimer Disease in Osaka (29). After an initial dose adjustment phase of 1 or 2 weeks, 163 patients with mild to moderately severe AD as staged by the NINCS-ADRDA criteria were randomized to receive maintenance doses of either 22.5, 30.0 or 45 mg/day galanthamine or placebo for 10 weeks. Therapeutic effects were assessed by ADAS, CIBIC+ and Activity of Daily Living scales. Drug monitoring covered hematology and clinical chemistry.

Clinically significant improvements (5 ADAS-Cog points more than with placebo) were seen with 30 and 45 mg/day galanthamine, while the placebo group deteriorated by 2.6 points. The side effect profile was reported as consistent with prior experiences, with adverse events related to cholinergic symptoms and mostly occurring during the dose adjustment phase. Although not yet completed, this study seems very promising because it involves a significant number of patients and multiple dose groups.

Data on long-term (> 12 months) use of galanthamine in AD were not available until very recently, when interim results from an open, 3-year follow-up evaluation of patients who had enrolled in one of the earlier trials were reported (30). Patients who received galanthamine with or without additional non-AChEI treatment had a significantly lower rate of cognitive decline as compared to the group with only non-AChEI therapy (which included medications such as nootropics and antidepressants). The degree of cognitive stabilization achieved within the first year of galanthamine therapy was found to be a good predictor of the 3-year outcome. Although efficacy of treatment had started to wear off at 24 months, a benefit from galanthamine treatment was shown by a rightward shift of the ADAS cognitive performance curve even at 36 months (Fig. 3). This is strikingly similar to findings reported for prolonged

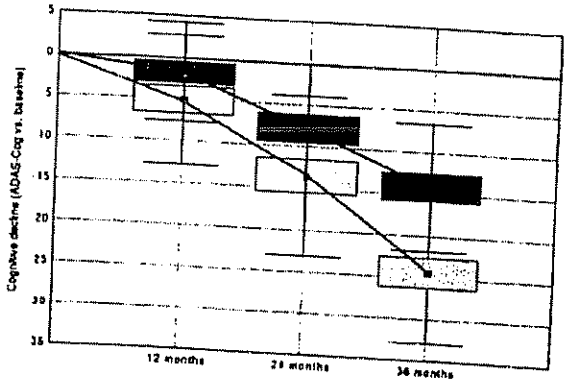

Fig. 3. 3-year cognitive performance profiles of 21 AD patients receiving galanthamine in addition to nootropic and antidepressant drugs (shaded boxes), compared to a matched group of 23 AD patients receiving no galanthamine or other acetylcholinesterase inhibitors. Boxes represent standard errors; error bars represent standard deviations.

tacrine therapy (31). It is also reassuring that, even after extended treatment, no clinically significant alterations in clinical laboratory parameters were observed.

Conclusions

After 10 years of clinical use of galanthamine in Alzheimer's disease, it seems appropriate to look back at the accomplishments of this past decade.

Several important issues must be kept in mind before results from controlled clinical evaluations of galanthamine in AD are compared with those from the much broader studies that have been conducted with tacrine. First, it is difficult to judge how closely the patients enrolled in the early galanthamine pilot studies would match today's criteria for primary degenerative dementia, as clinical diagnosis at that time was reported to be only about 85% specific for AD (32, 33). However, the results of these early investigations are generally in line with those obtained with better defined AD patients at a later date. While hepatotoxicity and other side effects prevented the majority of patients reaching or maintaining the 160 mg/day tacrine regimen that has been shown to achieve optimal cognitive improvement (13), as many as 78% of the participants tolerated their individual best dose of galanthamine in the first multicenter, double-blind study. This was probably the reason why the outcome regarding the primary variables, ADAS-Cog and Clinical Global Impression, was so impressive.

From the clinician's point of view, galanthamine is a reasonable approximation of the ideal concept of symptomatic AD therapy. While it is certainly superior to tacrine in terms of pharmacology and toxicity, one would, however, still hope that a presentation could be developed that would achieve sufficiently constant levels of acetylcholinesterase inhibition with once-daily medication. This might be accomplished by an oral sustained-release formulation or by a transdermal patch (34). Also, derivatives of galanthamine (35, 36) or from intermediates in chemical synthesis might pave the way to this goal.

In the literature there is still a dire lack of well-designed and controlled clinical studies with galanthamine hydrobromide, particularly concerning its long-term use, dose relationships and its interaction with other drugs commonly used in demented and multimorbid populations. However, even now galanthamine has an excellent safety record and has so far provided very promising evidence for its efficacy in mild or moderate AD. A notable absence of cumulative side effects, especially as far as hepatotoxicity is concerned, should offer a favorable alternative to tacrine therapy which requires monitoring of liver parameters – a challenging restriction for many elderly patients and their caregivers. With few restrictions to be observed and only moderate efficacy masking from drug side effects, as many as 50% of patients with primary degenerative dementia of Alzheimer's type could profit from treatment with galanthamine.

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EXHIBIT E

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EXHIBIT F

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EXHIBIT G

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE: '318 PATENT INFRINGEMENT LITIGATION	)	**REDACTED PUBLIC VERSION**
	)	Civil Action No. 05-356-SLR (consolidated)

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Dated: April 10, 2007

TABLE OF CONTENTS

Tab 5

> technological facts are known to those in the field of the invention, albeit not known to judges. (Citation omitted)

Discovision Assocs. v. Disc Mfg., Inc., 25 F. Supp. 2d 301, 344 (D. Del. 1998). Moreover, "inherent anticipation does not require a person of ordinary skill in the art to recognize the inherent disclosure in the prior art at the time the prior art is created" but rather when the patent application is filed. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed Cir. 2005).

Next, an anticipating reference "need not recite the elements of the patent claim in language identical to the language used in the claim, so long as the reference teaches the entirety of the invention." *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp 2d 479, 485 (D. Del. 2006). The Federal Circuit has explained that "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art." *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1382 (Fed. Cir. 2006). "Recognition of the inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation." *Matsushita Elec.*, 299 F. Supp. 2d at 362 (citing *Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003)). In addition, "[a] reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." *Celeritas Techs. v Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998) (citation omitted).

B. Whether the Asserted Claims of U.S. Patent No. 4,663,318 are Invalid for Obviousness Under 35 U.S.C. § 103

35 U.S.C. § 103 provides, *inter alia*, that a patent may not be obtained if the differences between the subject matter sought to be patented and the prior art would

have been obvious to a person having ordinary skill in the art. *Graham v. John Deere Co*., 383 U.S. 1 (1966). The question of whether a claimed invention is unpatentable as obvious under 35 U.S.C. § 103 is a question of law based on underlying findings of fact. *McNeil-PPC, Inc. v. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003). The underlying factual inquiries are: 1) the level of ordinary skill in the pertinent art at the time of the invention; (2) the scope and content of the prior art; (3) the differences, if any, between the claimed invention and the prior art; and (4) secondary considerations, if any, of non-obviousness. *Graham*, 383 U.S. at 17-18; *McNeil-PPC*, 337 F.3d at 1368. Although the United States Supreme Court[1] is considering a case in which the obviousness standard is at issue, currently a party has to demonstrate a motivation or suggestion to combine or modify prior art references to produce the claimed invention, coupled with a reasonable expectation of success. *Brown and Williamson Tobacco Corp. v. Phillip Morris Inc.*, 229 F.3d 1120, 1124-25 (Fed. Cir. 2000).

1. **Level of Ordinary Skill in the Art**

35 U.S.C. § 103 requires that a claim be declared invalid when the invention set forth in the claim can be said to have been obvious to one of ordinary skill in the art to which the patent pertains. *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). In determining the level of ordinary skill in the art, a court should consider the following factors relevant to the inquiry: 1) educational level of the inventor; 2) type of problems encountered in the art; 3) prior art solutions; 4) rapidity of innovation; 5)

[1] The United States Supreme Court currently (oral argument is complete) is deciding *KSR Int'l. Co. v. Teleflex, Inc.*, Docket No. 04-1350, where the issue is whether the Federal Circuit erred in holding that a claimed invention cannot be held obvious in the absence of some "teaching, suggestion, or motivation" that would have led one of ordinary skill in that art to combine the relevant prior art in the manner claimed. That decision likely will have a significant impact on the law of obviousness and, thus, an impact on the Court's decision here

sophistication of technology; and 6) educational level of active workers in the field. *Envtl Designs, Ltd. v. Union Oil Co*, 713 F.2d 693, 697 (Fed. Cir. 1983). "[N]ot all of the factors listed above may be present in every case, and one or more of these or other factors may predominate in a particular case." *Id.* at 696-97. This hypothetical person of ordinary skill in the art is presumed to know all of the teachings of the prior art references in the field of the invention at the time the invention was made. *Union Carbide Corp. v. Am. Can Co.*, 724 F.2d 1567, 1576 (Fed. Cir. 1984).

"The fact of near-simultaneous invention, though not determinative of statutory obviousness, is strong evidence of what constitutes the level of ordinary skill in the art." *Ecolochem, Inc. v. S. Cal. Edison, Co.*, 227 F.3d 1361, 1379 (Fed. Cir. 2000) (citation omitted). In fact, "[t]he issue of simultaneous invention is *directly tied* to the level of knowledge attributable to one of ordinary skill in the art." *Id.* (emphasis added); *see also Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 883 (Fed. Cir. 1998) (citing *In re Merck & Co.*, 800 F.2d 1091, 1098 (Fed. Cir. 1986) and *Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 906 (Fed. Cir. 1986)) (recognizing "the relevance of contemporaneous independent invention to the level of ordinary knowledge or skill in the art").

2. **The Scope and Content of the Prior Art**

In determining whether the claimed invention falls within the scope of the relevant prior art, a court first examines "the field of the inventor's endeavor" and "the particular problem with which the inventor was involved" at the time the invention was made. *Monarch Knitting*, 139 F.3d at 881 (Fed. Cir. 1998). Prior art references which are not within the field of the inventor's endeavor may still properly be considered to fall

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EXHIBIT J

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EXHIBIT M

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